D1

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
1 August 2002 (01.08.2002)

PCT

(10) International Publication Number
WO 02/059089 A2

(51) International Patent Classification[7]: C07D 209/12, 209/88, 405/12

(21) International Application Number: PCT/EP02/00583

(22) International Filing Date: 22 January 2002 (22.01.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
01101584.9 25 January 2001 (25.01.2001) EP

(71) Applicant: F. HOFFMANN-LA ROCHE AG [CH/CH]; 124, Grenzacherstrasse, CH-4070 Basle (CH).

(72) Inventors: SCALONE, Michelangelo; 14, Baslerstrasse, CH-4127 Birsfelden (CH). ZEIBIG, Thomas; 3, Schlesierstrasse, 67112 Mutterstadt (DE).

(74) Agent: WITTE, Hubert; 124 Grenzacherstrasse, CH-4070 Basle (CH).

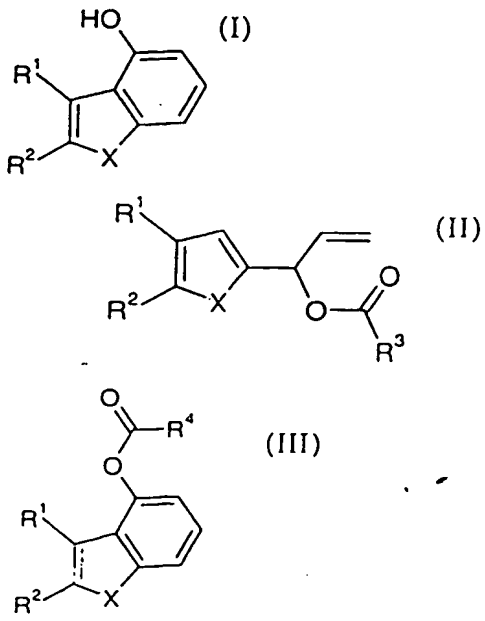
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PROCESS FOR THE PREPARATION OF HETEROCYCLIC INDENE ANALOGS



(57) Abstract: The present invention is concerned with a novel process for the preparation of compounds of formula (I) wherein R^1, R^2 and X are as defined in the specification, comprising cyclocarbonylation of a compound of formula (II) wherein R^1, R^2, R^3 and X are as defined in the specification, to produce a compound of formula (III) wherein R^1, R^2, R^4 and X are as defined in the specification, followed by saponification.

WO 02/059089 A2

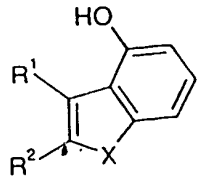
Process for the preparation of heterocyclic indene analogs

The present invention is concerned with a novel process for the preparation of heterocyclic indene analogs, especially with the preparation of 4-hydroxycarbazole or N-protected 4-hydroxycarbazole. These compounds may be used as a building block for pharmaceutically active compounds, e.g. 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxy-phenoxy)ethyl]amino]-2-propanol (carvedilol). This compound is known in the art and is described for example in EP 0 004920. It is especially useful for prophylaxis and treatment of heart- and circulatory diseases like, for example, hypertension, coronary heart failure, angina pectoris and the like.

Methods for the catalytic cyclocarbonylation of pyrrole and indole derivatives have been described by Hiday et al., Advances in Metal-Organic Chemistry, Volume 4, 275-309. These processes are characterized by high temperatures, high catalyst loadings and modest selectivity. Moreover, the educts necessary for the said reactions are expensive, since they have to be prepared by lengthy procedures, and are not available commercially.

Surprisingly, it has been found that using the process according to the present invention, heterocyclic indene analogs, e.g. indole or carbazole derivatives (such as 4-hydroxycarbazole and N-protected 4-hydroxycarbazole) can be prepared from commercial educts and without the aforementioned disadvantages.

The present invention refers to a process for the preparation of heterocyclic indene analogs of formula (I)



(I)

wherein

R^1 and R^2 are independently selected from hydrogen or lower-alkyl; or

R^1 and R^2 together with the ring carbon atoms to which they are attached form a monovalent carbocyclic or a phenyl ring, wherein the said monovalent carbocyclic or phenyl ring may optionally be substituted by halogen, lower-alkyl or lower-alkoxy;

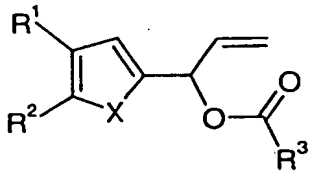
X is O, S or N-Z;

Z is an amino protecting group selected from SO_2R^a, NMe_2, CO_2R^b and $CON(R^c)_2$; and

R^a is lower-alkyl or aryl;

R^b and R^c are lower-alkyl;

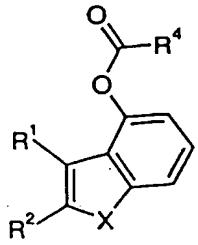
said process comprising cyclocarbonylation of a compound of formula (II)



(II)

wherein R^3 is lower-alkyl, aryl or aralkyl and R^1, R^2 and X are as defined above;

to produce a compound of formula (III)



(III)

wherein R^4 is lower-alkyl or aryl and R^1, R^2 and X are as defined above;

followed by saponification.

This process provides an efficient cyclocarbonylation reaction under mild conditions. In addition, substrates for the cyclocarbonylation reaction (compound of formula (II)) do not need to be purified, e.g. by crystallization or distillation, but can be used as "crude" material.

According to the present invention, the term "cyclocarbonylation" refers to an introduction of a carbonyl group coupled to the formation of an aromatic cyclic ring structure.

The term "transition metal compound" refers to a metal-phosphine complex compound wherein the term metal refers to Pd, Pt, Ru, Co, Rh or Ni, preferably Pd.

The term "ligand" refers to phosphine, arsine or stibine derivatives, preferable phosphine derivatives, of general formulae $P(R^5)(R^6)(R^7)$, $(R^5)(R^6)P\text{-}(X)\text{-}P(R^5)(R^6)$, $As(R^5)(R^6)(R^7)$ or $Sb(R^5)(R^6)(R^7)$, preferably $P(R^5)(R^6)(R^7)$, wherein R^5, R^6, and R^7 are defined below.

The term "alkyl" refers to a branched or straight chain monovalent alkyl radical of one to nine carbon atoms (unless otherwise indicated). The term "lower-alkyl" refers to a branched or straight chain monovalent alkyl radical of one to four carbon atoms. This term is further exemplified by such radicals as methyl, ethyl, n-propyl, isopropyl, i-butyl, n-butyl, t-butyl and the like.

The term "alkoxy", alone or in combination, signifies a group of the formula alkyl-O- in which the term "alkyl" has the significance given above. Examples of such "alkoxy" radicals are methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec.butoxy and tert.butoxy, preferably methoxy and ethoxy.

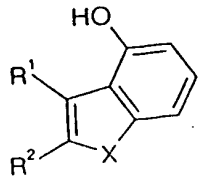
The term "aryl" refers to a monovalent carbocyclic aromatic radical, e.g. phenyl or naphthyl, optionally substituted, independently, with halogen, lower-alkyl, lower-alkoxy, lower-alkylenedioxy, carboxy, trifluoromethyl and the like.

The term "aralkyl" refers to a residue $-CH_2$-aryl wherein the term aryl is as defined above.

The term "alkylenedioxy" refers to C_{1-3}-alkyl-dioxy groups, such as methylene-dioxy, ethylenedioxy or propylenedioxy.

The term "halogen" refers to fluorine, chlorine, and bromine.

In more detail, the present invention refers to a process for the preparation of compounds of formula (I)



(I)

wherein

R^1 and R^2 are independently selected from hydrogen or lower-alkyl; or

R^1 and R^2 together with the ring carbon atoms to which they are attached form a monovalent carbocyclic or phenyl ring, wherein the said monovalent carbocyclic or phenyl ring may optionally be substituted by halogen, lower-alkyl or lower-alkoxy;

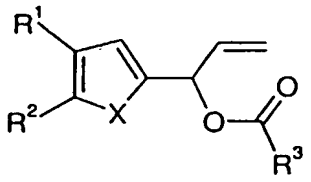
X is O, S or N-Z;

Z is an amino protecting group selected from SO_2R^a, NMe_2, CO_2R^b and $CON(R^c)_2$; and

R^a is lower-alkyl or aryl;

R^b and R^c are lower-alkyl;

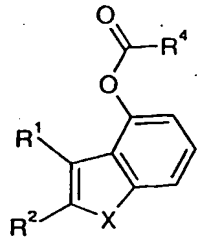
said process comprising cyclocarbonylation of a compound of formula (II)



(II)

wherein R^3 is lower-alkyl, aryl or aralkyl and R^1, R^2 and X are as defined above;

to produce a compound of formula (III)



(III)

wherein R^4 is lower-alkyl or aryl and R^1, R^2 and X are as defined above;

followed by saponification.

Examples of lower-alkyl residues R^1 and R^2 are methyl, ethyl, n-propyl and isopropyl, with methyl being preferred. Preferred monovalent carbocyclic rings formed by substituents R^1 and R^2 together with the ring carbon atoms to which they are attached are cyclopentenyl, cyclohexenyl and cycloheptenyl, preferably cyclohexenyl. Such rings may be substituted by lower-alkyl, such as methyl and ethyl. The most preferable monovalent carbocyclic ring formed by substituents R^1 and R^2 together with the ring carbon atoms to which they are attached is unsubstituted cyclohexenyl. A phenyl residue formed by R^1 and

R^2 together with the ring carbon atoms to which they are attached may be substituted by halogen, lower-alkyl or lower-alkoxy, preferably by chloro, bromo, methyl or methoxy. Most preferably, R^1 and R^2 together with the ring carbon atoms to which they are attached form an unsubstituted phenyl ring.

Examples of aryl residues in substituent R^3 are phenyl and phenyl substituted by halogen or lower alkyl, preferably unsubstituted phenyl. Preferable aralkyl residue R^3 is benzyl, optionally substituted by halogen or lower alkyl. Most preferable aralkyl residue R^3 is unsubstituted benzyl. Examples of lower-alkyl residues R^3 are methyl, ethyl, n-propyl, isopropyl and t-butyl, with methyl being preferred.

R^4 depends on the anhydride used in the cyclocarbonylation reaction. Examples of lower-alkyl residues are methyl, ethyl, n-propyl, isopropyl and t-butyl, with methyl being preferred. An example of aryl residues is phenyl. Such phenyl residue may be substituted by halogen, lower-alkyl or lower-alkoxy, preferably by chloro, bromo, methyl or methoxy. The most preferable aryl residue R^4 is unsubstituted phenyl.

Examples of lower-alkyl residues R^a, R^b and R^c are methyl, ethyl, n-propyl, isopropyl and t-butyl, with methyl being preferred. Examples of aryl residues R^a are phenyl and naphthyl. Such rings may be substituted by halogen or lower-alkyl, preferably by chloro, methyl, ethyl or isopropyl. More preferably, aryl residue R^a is phenyl, substituted by halogen or lower-alkyl, preferably by chloro, methyl, ethyl or isopropyl. Most preferred aryl residue R^a is phenyl.

In another preferred embodiment, the present invention relates to a cyclocarbonylation process as described above, wherein R^1 and R^2 together with the ring carbon atoms to which they are attached form a phenyl ring, R^3 is methyl or phenyl, X is N-Z, Z is an amino protecting group as defined above, preferably a group of the formula SO_2R^a wherein R^a is phenyl.

In a preferred embodiment of the invention, the cyclocarbonylation reaction is carried out in the presence of a base, an anhydride and a catalyst comprising a transition metal compound and a ligand.

Transition metal compounds useful for the process of the present invention comprise salts of Pd, Pt, Ru, Co, Rh or Ni and also includes Pd/C. The use of transition metal compounds as catalysts has been described for example in Matsuzaka et al. (1988) J. Org. Chem. 53, 3832. Preferred transition metal compounds are salts of palladium, e.g. $Pd(OAc)_2$, Pd_2dba_3, $PdCl_2$, $Pd_2Cl_2(\pi\text{-allyl})_2$, $PdCl_2(NCMe)_2$, $[Pd(NCMe)_4](BF_4)_2$, and most preferably $Pd(OAc)_2$. The mentioned catalysts are known in the art (e.g. US Patent No. 5,380,861; "Carbonylation, Direct Synthesis of Carbonyl Compounds", H.M. Colquhoun,

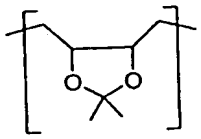
D.J. Thompson, M.V. Trigg, Plenum Press, 1991) and/or are commercially available (e.g. from Fluka, Buchs, Switzerland or Strem Chemicals, Kehl, Germany).

The ligand of the transition metal compound in the catalyst may be selected from a group consisting of phosphine, arsine or stibine derivatives, preferably phosphine derivatives of general formulae $P(R^5)(R^6)(R^7)$, $(R^5)(R^6)P\text{-}(Y)\text{-}P(R^5)(R^6)$, $As(R^5)(R^6)(R^7)$ or $Sb(R^5)(R^6)(R^7)$, preferably $P(R^5)(R^6)(R^7)$, wherein Y, R^5, R^6, and R^7 are defined below.

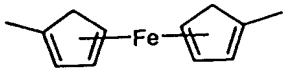
Especially suitable ligands are chiral and non-chiral mono- and diphosphorus compounds for example described in Houben-Weyl, "Methoden der organischen Chemie", vol. E1, page 106 et seq. Georg Thieme Verlag Stuttgart, 1982, and Aspects Homog. Catal., 4, 145-202 (1981), especially those of the formulae

$$P(R^5)(R^6)(R^7) \text{ and } (R^5)(R^6)P\text{-}(Y)\text{-}P(R^5)(R^6)$$

wherein R^5, R^6 and R^7 each independently are C_{1-8}-alkyl, cyclohexyl, benzyl, naphthyl, 2- or 3-pyrrolyl, 2- or 3-furyl, 2- or 3-thiophenyl, 2- or 3- or 4-pyridyl, phenyl or phenyl which is substituted by C_{1-4}-alkyl, C_{1-4}-alkoxy, halogen, trifluoromethyl, lower-alkylydenedioxy or phenyl and Y is binaphthyl, 6,6'-dimethyl- or 6,6'-dimethoxybiphenyl-2,2'-diyl, or one of the groups $-(CH_2)_n-$, $-CH_2CH_2-P(C_6H_5)-CH_2CH_2-$,



or

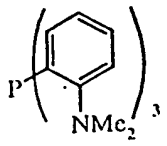


(IV)

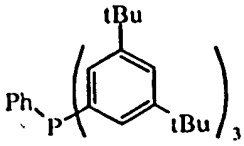
and n is a number of 1 – 8.

Examples of suitable phosphorus ligands are triphenylphosphine and the ligands shown in Scheme 1.

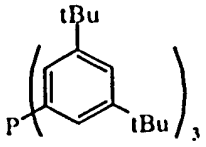
Scheme 1:



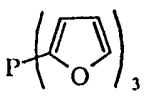
P(o-DMA-Ph)$_3$



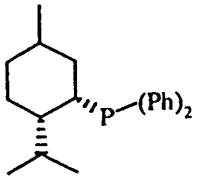
PPh(3,5-tBu-Ph)$_2$



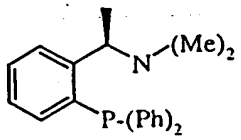
P(3,5-tBu-Ph)$_3$



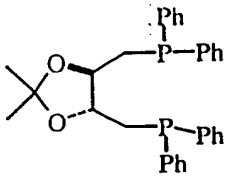
P(2-Furyl)$_3$



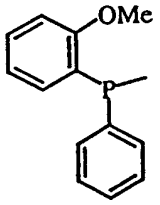
NMDPP



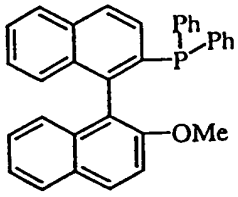
AMPHOS



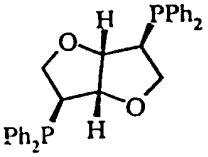
DIOP



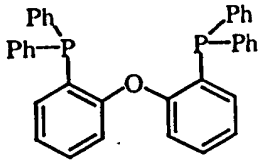
PAMP



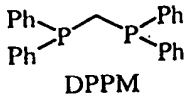
MOP



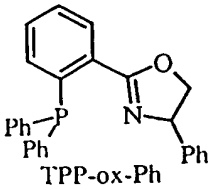
(S,S)-DDPPI



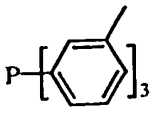
DPEphos



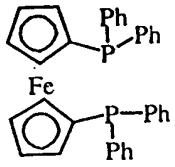
DPPM



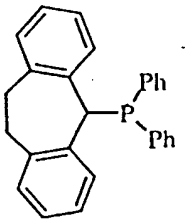
TPP-ox-Ph



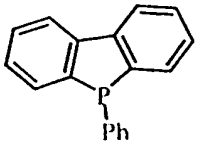
P(m-Tol)$_3$



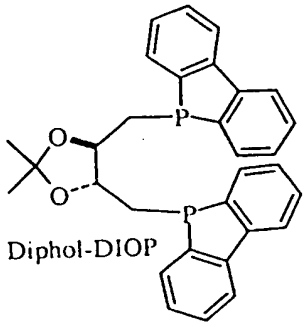
DPPF



TROPP-Ph

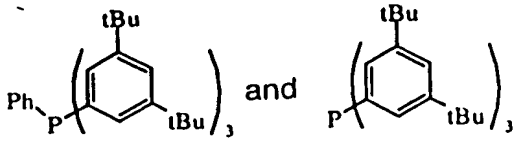


PPh(Diphol)



Diphol-DIOP

Preferred phosphorus ligands are triphenylphosphine,



$PPh(3,5\text{-}tBu\text{-}Ph)_2$ $P(3,5\text{-}tBu\text{-}Ph)_3$,

the most preferred phosphorus ligand is triphenylphosphine.

The preparation of a transition metal complex is explained in more detail for the corresponding palladium-phosphine complex: The palladium-phosphine complex compound is conveniently formed in situ from a palladium component and a phosphine ligand. These palladium components is for example metallic palladium, which is optionally supported on a carrier material such as carbon, or a complex or a salt of 0-, 2- or 4-valent palladium such as palladium-bis(dibenzylideneacetone), palladium chloride, palladium acetate and the like. For the in situ preparation, the phosphorus ligand/transition metal compound ratio (mol/mol; P/Pd) amounts to about 0.1 : 1 to 100 : 1, preferably to about 6 : 1 to 15 : 1. Suitable phosphine ligands are for example chiral and non-chiral mono- and diphosphorus compounds such as are described in Houben-Weyl, Methoden der organischen Chemie, volume E1, page 106 et. seq. Georg Thieme Verlag Stuttgart, 1982, and Aspects Homog. Catal., 4, 145 – 202 (1981), especially those described above.

For the in situ preparation of the palladium-phosphine complex compound palladium-(II) chloride or palladium-(II) acetate, palladium-dichloro-bis(acetonitrile) and triarylphosphine may be used.

Further, the process of the present invention comprises the use of bases for the cyclocarbonylation reaction like tertiary bases such as tri-alkyl-amines, di-alkyl-aryl-amines, pyridines, alkyl-N-piperidines, and for example inorganic bases such as NaOH, KOH or salts of carbonic acids. Examples are $(alkyl)_3$amines, e.g. triethylamine, ethyl-di-isopropyl-amine, pyridine, N-methyl-piperidine, sodium hydrogen carbonate, potassium hydrogen carbonate, di-sodium carbonate, etc. The preferred base is triethylamine.

The process of the present invention also comprises the use of an anhydride of the formula $(R^4(C=O))_2O$ for the cyclocarbonylation reaction. Examples of anhydrides in connection with the present invention are acetic anhydride, propionic anhydride, butyric anhydride, isobutyric anhydride, pivalic anhydride, benzoic anhydride etc. The preferred anhydrides are acetic anhydride and benzoic anhydride.

Solvents for the above reaction are known to skilled persons. Preferred solvents are aromatic solvents, e.g. toluene, xylene, benzene, halogenated hydrocarbons, e.g. CH_2Cl_2,

nitriles, e.g. acetonitrile, ester, e.g. ethylacetate, amides, e.g. DMF, ether, e.g. THF, dioxane, urethanes, e.g. TMU, sulfoxides, e.g. DMSO, and mixtures thereof. The preferred solvent is toluene.

The reaction conditions for the above carbonylation reaction can vary to a certain extent.

The temperature can vary between 40°C and 170°C, preferably between 60 – 120°C, and most preferably the reaction is performed at about 90°C.

The substrate/catalyst ratio (mol/mol; S/Pd) amounts to 1 to 10000, preferably 100 to 5000, more preferably 100 to 1500 and most preferably 100 to 1000.

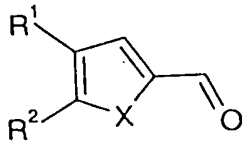
For the in situ preparation, the above mentioned phosphorus ligand/transition metal compound ratio (mol/mol; P/Pd) amounts to 0.1 : 1 to 100 : 1, preferably 6 : 1 to 15 : 1.

The upper limit for the carbon monoxide (CO) pressure is only limited by the specification of the autoclave used. For the lower pressure limit the carbonylation reaction would work even with a CO pressure of 1 bar. Preferably, the CO pressure is about 20 to 70 bar, more preferably 35 to 60 bar.

It has been found that the "crude" compound of formula (II) can be used for the preparation of the compound of formula (I). A preparation of a crude material is performed by collecting a compound of formula (II), e.g. acetic acid 1-(1-benzenesulfonyl-1H-indol-2-yl)-allyl ester, with an organic solvent and drying without further purification. The preparation of this material is exemplified in Examples 2 and 3, Example 5 shows the use of the crude starting material for the preparation of a compound of formula (I).

The cyclocarbonylation reaction is followed by saponification. Conditions for saponification reactions are known in the art and described for example in "Practical Organic Chemistry", A.I. Vogel, Longmans Ed., 1967, p. 390 – 393. In a preferred embodiment of the present invention, the saponification is carried out in a biphasic mixture of aqueous sodium hydroxide and toluene or in an homogeneous mixture of sodium methylate in methanol.

Compounds of formula (II) may be prepared by methods known in the art, for example by reaction of compounds of formula (V)

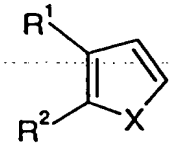


(V)

wherein R^1, R^2 and X are as defined above;

with a reagent of the formula vinyl-metal-X with –metal-X being –MgCl, -MgBr, -MgI or -Li, followed by reaction with an acid derivative selected from a group consisting of $(R^3\text{-CO})_2O$, or $R^3\text{-(CO)-Hal}$, wherein R^3 is as defined above and Hal is Cl or Br.

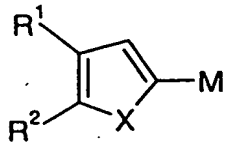
Compounds of formula (V) are commercially available or can be prepared from compounds of formula (Va)



(Va)

by methods known in the art.

Preferably, the compounds of formula (II) may be prepared by reaction of compounds of formula (VI)

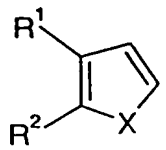


(VI)

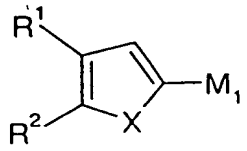
wherein R^1, R^2 and X are as defined above and M is –MgCl, -MgBr, -MgI or –Li;

with acrolein, followed by reaction with an acid derivative selected from a group consisting of $(R^3\text{-CO})_2O$ or $R^3\text{-(CO)-Hal}$, wherein R3 is as defined above and Hal is Cl or Br.

Compounds of formula (VI) are commercially available or can be prepared from compounds of formula (VIa) or compounds of formula (VIb)



(VIa)



(VIb)

wherein M_1 is chloro, bromo or iodo;

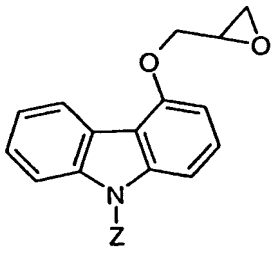
by methods known in the art.

In a preferred embodiment, the present invention relates to a process for the preparation of 4-hydroxycarbazole or N-protected 4-hydroxycarbazole. N-protected 4-hydroxycarbazole can be prepared by a cyclocarbonylation reaction as described above starting from a compound of above formula (II), wherein R^1 and R^2 together with the ring carbon atoms to which they are attached form a phenyl ring, R^3 is as defined above , X is

N-Z and Z is an amino protecting group selected from SO_2R^a, NMe_2, CO_2R^b and $CON(R^c)_2$ (with R^a, R^b and R^c being as defined above), in the presence of an anhydride and a base as defined above, followed by saponification. N-protected 4-hydroxycarbazole can be converted to 4-hydroxycarbazole by deprotection as described below. 4-Hydroxycarbazole and N-protected 4-hydroxycarbazole are useful for the preparation of pharmaceutically active substances, e.g. 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-2-propanol (carvedilol) and optionally salts thereof. A process for the preparation of this compound has been described for example in European Patent Application EP 0 004920.

In addition, this compound may be prepared according to the following processes:

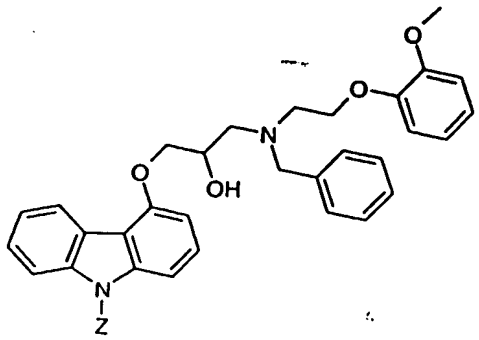
In a first step, a compound of above formula (I), wherein R^1 and R^2 together with the ring carbon atoms to which they are attached form a phenyl ring, X is N-Z and Z is an amino protecting group selected from SO_2R^a, NMe_2, CO_2R^b and $CON(R^c)_2$ (with R^a, R^b and R^c being as defined above), may be converted into a compound of formula (VII)



(VII)

wherein Z is as defined above, by reaction with epichlorohydrin under basic conditions. The reaction may be performed in polar organic solvents like THF, DMF or DMSO, preferably without a solvent in a great surplus of epichlorohydrin. Basic compounds are for example sodium carbonate, potassium carbonate, sodium hydride, potassium hydroxide and sodium hydroxide, preferably sodium hydroxide. The temperature can vary between 20°C and 100°C, with a preferred temperature between 40– 60°C.

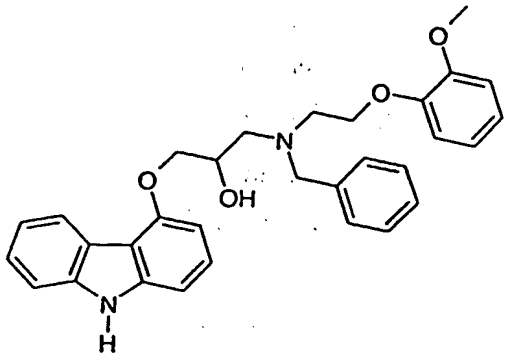
The above process may be followed by conversion of the compound of formula (VII) into a compound of formula (VIII)



(VIII)

wherein Z is as defined above, by reaction with benzyl-[2-(2-methoxy-phenoxy]-ethyl-amine. The reaction may be performed in organic solvents like ethanol, methanol, isopropanol, THF and DMF, preferably with ethanol. The temperature can vary between 40 and 140°C, with a preferred temperature between 60-90°C.

Deprotection of the compound of formula (VIII) reveals 1-{benzyl-[2-(2-methoxy-phenoxy)-ethyl]-amino}-3-(9H-carbazol-4-yloxy)-propan-2-ol of formula (IX)

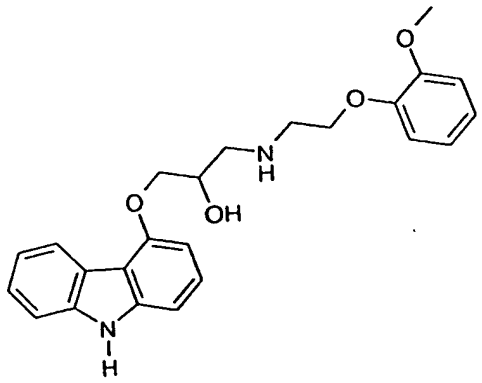


(IX)

Methods of deprotection reactions are known in the art and described for example in P.J.Kocienski, Protecting Groups, Thieme 1994. From a compound of above formula (VIII) for example, wherein Z is SO_2R^a and R^a is phenyl, 1-{benzyl-[2-(2-methoxy-phenoxy)-ethyl]-amino}-3-(9H-carbazol-4-yloxy)-propan-2-ol of formula (IX) can be synthesized under basic conditions in organic solvents like ethanol, methanol, isopropanol, THF and DMF or mixtures of these solvents, preferably with a mixture of THF and methanol. Basic compounds are for example potassium hydroxide, sodium hydroxide and potassium tert-butoxide, preferably sodium hydroxide. The temperature can vary between 20°C and 100°C, with a preferred temperature between 40– 60°C.

Hydrogenation of the compound of formula IX reveals 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-2-propanol (carvedilol) of formula (X). The reaction may be performed in organic solvents like ethanol, methanol, isopropanol and THF, preferably with methanol. The pressure of hydrogen can vary between 1 bar and 50

bar pressure, with a preferred hydrogen pressure between 1 to 10 bar. The temperature can vary between 20°C and 100°C, with a preferred temperature between 40– 60°C.



(X)

Another embodiment of the present invention relates to a process for the preparation of 1-(9H-carbazol-4-yloxy)-3-{[2-(2-methoxyphenoxy)ethyl]amino}-2-propanol comprising:

a) cyclocarbonylation of acetic acid 1-(1-benzenesulfonyl-1H-indol-2-yl)allyl ester or benzoic acid 1-(1-benzenesulfonyl-1H-indol-2-yl)-allyl ester to give acetic acid 9-benzenesulfonyl-9H-carbazol-4-yl ester;

b) saponification of acetic acid 9-benzenesulfonyl-9H-carbazol-4-yl ester to give 9-benzenesulfonyl-9H-carbazol-4-ol;

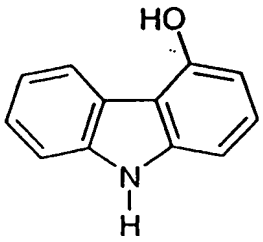
c) reaction of 9-benzenesulfonyl-9H-carbazol-4-ol with epichlorohydrin under basic conditions to give 9-benzenesulfonyl-4-oxiranylmethoxy-9H-carbazole;

d) reaction of 9-benzenesulfonyl-4-oxiranylmethoxy-9H-carbazole with benzyl-[2-(2-methoxy-phenoxy]-ethyl-amine to give a 1-(9-benzenesulfonyl-9H-carbazol-4-yloxy)-3-{benzyl-[2-(2-methoxy-phenoxy)ethyl]-amino}-propan-2-ol;

e) deprotection of 1-(9-benzenesulfonyl-9H-carbazol-4-yloxy)-3-{benzyl-[2-(2-methoxy-phenoxy)ethyl]-amino}-propan-2-ol under basic conditions to give 1-{benzyl-[2-(2-methoxy-phenoxy)-ethyl]-amino}-3-(9H-carbazol-4-yloxy)-propan-2-ol;

f) hydrogenation of 1-{benzyl-[2-(2-methoxy-phenoxy)-ethyl]-amino}-3-(9H-carbazol-4-yloxy)-propan-2-ol in an organic solvent to give 1-(9H-carbazol-4-yloxy)-3-{[2-(2-methoxyphenoxy)ethyl]amino}-2-propanol of formula (X).

The above process for the preparation of 1-(9H-carbazol-4-yloxy)-3-{[2-(2-methoxyphenoxy)ethyl]amino}-2-propanol (carvedilol) may alternatively be performed in an analogous manner starting from 4-hydroxycarbazole of formula (XI)

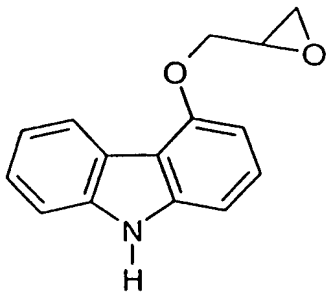


(XI)

instead of N-protected 4-hydroxycarbazole.

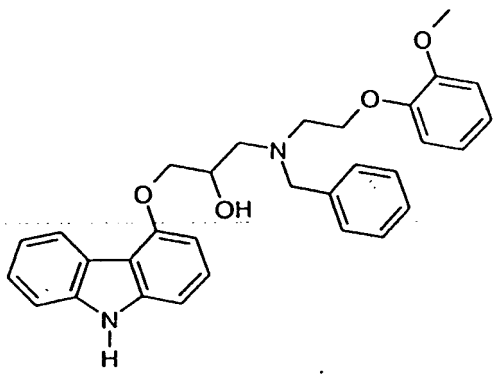
A compound of above formula (I), wherein R^1 and R^2 together with the ring carbon atoms to which they are attached form a phenyl ring, X is N-Z and Z is an amino protecting group selected from SO_2R^a, NMe_2, CO_2R^b and $CON(R^c)_2$ (with R^a, R^b and R^c being as defined above), may be converted into 4-hydroxycarbazole formula (XI) by deprotection. Methods of deprotection reactions are known in the art and described for example in P.J.Kocienski, Protecting Groups, Thieme 1994. From a compound of above formula (I) for example, wherein R^1 and R^2 together with the ring carbon atoms to which they are attached form a phenyl ring, X is N-Z, Z is SO_2R^a and R^a is phenyl, 4-hydroxy-carbazole can be synthesized under basic conditions in organic solvents like ethanol, methanol, isopropanol, THF and DMF or mixtures of these solvents, preferably with THF. Basic compounds are for example potassium hydroxide, sodium hydroxide, sodium methoxide, sodium tert.-butoxide and potassium tert.-butoxide, preferably potassium tert.-butoxide. The temperature can vary between 10°C and 100°C, with a preferred temperature between 20°C and 40°C.

4-hydroxy-carbazole (XI) may be converted into a compound of formula (XII) by reaction with epichlorohydrin under basic conditions. The reaction may be performed in polar organic solvents like THF, DMF or DMSO, preferably without a solvent in a great surplus of epichlorohydrin. Basic compounds are for example sodium carbonate, potassium carbonate, sodium hydride, potassium hydroxide and sodium hydroxide, preferably sodium hydroxide. The temperature can vary between 20°C and 100°C, with a preferred temperature between 40– 60°C.



(XII)

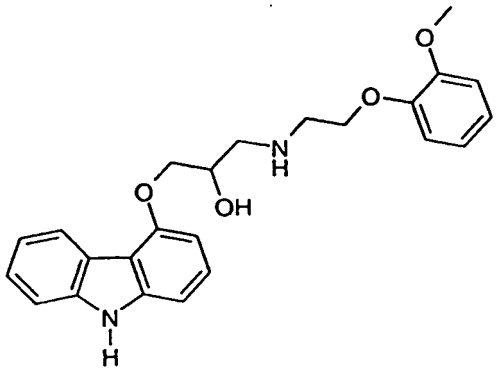
The above process may be followed by conversion of the compound of formula (XII) into a compound of formula (IX)



(IX)

by reaction with benzyl-[2-(2-methoxy-phenoxy]-ethyl-amine. The reaction may be performed in organic solvents like ethanol, methanol, isopropanol, THF and DMF, preferably with ethanol. The temperature can vary between 40 and 140°C, with a preferred temperature between 60-90°C.

Hydrogenation of the compound of formula IX reveals 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-2-propanol (carvedilol) of formula (X)



(X)

This reaction may be performed as described above.

Another embodiment of the present invention relates to a process for the preparation of 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-2-propanol comprising:

a) cyclocarbonylation of acetic acid 1-(1-benzenesulfonyl-1H-indol-2-yl)allyl ester or benzoic acid 1-(1-benzenesulfonyl-1H-indol-2-yl)-allyl ester to give acetic acid 9-benzenesulfonyl-9H-carbazol-4-yl ester;

b) saponification of acetic acid 9-benzenesulfonyl-9H-carbazol-4-yl ester to give 9-benzenesulfonyl-9H-carbazol-4-ol;

c) deprotection of 9-benzenesulfonyl-9H-carbazol-4-ol to give 4-hydroxy-carbazole

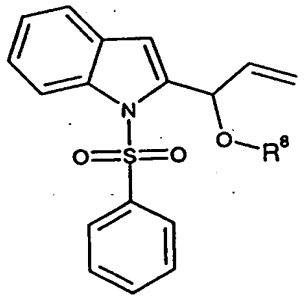
d) reaction of 4-hydroxy-carbazole with epichlorohydrin under basic conditions to give 4-oxiranylmethoxy-9H-carbazole;

e) reaction of 4-oxiranylmethoxy-9H-carbazole with benzyl-[2-(2-methoxy-phenoxy]-ethyl-amine to give a 1-{benzyl-[2-(2-methoxy-phenoxy)-ethyl]-amino}-3-(9H-carbazol-4-yloxy)-propan-2-ol;

f) hydrogenation of 1-{benzyl-[2-(2-methoxy-phenoxy)-ethyl]-amino}-3-(9H-carbazol-4-yloxy)-propan-2-ol in an organic solvent to give 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-2-propanol of formula (X).

In a further embodiment, the present invention relates to the use of any of the above processes for the preparation of 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)-ethyl]-amino]-2-propanol and optionally salts thereof.

The compounds of formula (IIa)



(IIa)

wherein R^8 is hydrogen, acetyl or benzoyl, are preferred educts of the processes according to the present invention. These compounds are new and are also subject of the present invention.

The following examples shall illustrate preferred embodiments of the present invention but are not intended to limit the scope of the invention.

EXAMPLES

Example 1

1-(1-Benzenesulfonyl-1H-indol-2-yl)-allyl alcohol

10.3 g (40 mmol) of 1-(phenylsulfonyl)indole (synthesized analogous to T. Sakamoto; Y. Kondo; N. Takazawa; H. Yamanaka; J.Chem.Soc.Perkin Trans.1; 16; 1996; 1927-1934) in 110 ml tetrahydrofuran were cooled to -20°C. To the stirred solution 30 ml of 1,6 M n-butyllithium were added at –20°C within 20 min. The resulting suspension was warmed to 10°C and stirred at 10°C for 4 hours. The mixture was again cooled to –20°C and a solution of 3.4 g acrolein (61 mmol) in 20 ml THF was added dropwise within 20 min at –20°C. The solution was stirred at 20°C for 16 hours. 150 ml water was added dropwise, the mixture was vigorously stirred for 10 min. The phases were separated, and the water phase was extracted with 3 x 100 ml of methyl-t-butyl-ether. The combined organic phases were washed with 100 ml of brine, dried on sodium sulfate and rotary evaporated (35°C, 20 mbar). The residue was purified by liquid chromatography (eluent toluene/ethyl acetate 6:1), the pure fractions were collected and rotary evaporated (40°C/15 mbar).

Yield: 10.0 g (80 %).

1H NMR (δ, DDMSO): 5.78 (OH, d), 5.86 (C<u>H</u>-O, dd), 6.20 (C<u>H</u>=CH2, ddd), 5.19 (CH=C<u>H</u>2, dd), 5.40 (CH=C<u>H</u>2, dd), aromatic signals at 6.7-8.1.

Example 2

Acetic acid 1-(1-benzenesulfonyl-1H-indol-2-yl)-allyl ester

To a solution of 19.1 g of 1-(1-benzenesulfonyl-1H-indol-2-yl)-allyl alcohol (74 mmol) in 244 ml dichloromethane were added 34 ml triethylamine and 0.7 g 4-dimethyl-aminopyridine. The solution was cooled to 3°C. To the magnetically stirred solution 23.5 ml of acetic anhydride qas added with a dropping funnel at a temperature below 5°C. The reaction mixture was stirred 2 h at 22°C. After cooling in an ice bath 250 ml of water was added at a temperature of 20 to 24°C. The mixture was vigorously stirred for 10 min. The phases were separated, and the water solution extracted with 250 ml of dichloromethane. The combined organic phases were extracted with 250 ml of water three times, and once with 250 ml of brine. The dichloromethane solution was dried on sodium sulfat and finally rotary evaporated (35°C, 50 mbar), yield 22.8 g. In the next step (the cyclocarbonylation) the resulting oil was used without purification (crude quality).

1H NMR (δ, DDMSO): 2.07 (CH3-CO, s), 6.87 (CH-O, d), 6.19 (CH=CH2, ddd), 5.37 (CH=CH2, dd), 5.38 (CH=CH2, dd), aromatic signals at 6.9-8.0.

Example 3

Benzoic acid 1-(1-benzenesulfonyl-1H-indol-2-yl)-allyl ester

To a stirred solution of 10.0 g of 1-(1-benzenesulfonyl-1H-indol-2-yl)-allyl alcohol (32 mmol) in 100 ml of pyridine were added dropwise 5,6 ml benzoyl chloride (48 mmol) at 10°C. The mixture was stirred for an additional 1 h at 20°C. Most of the pyridine was distilled off , the residue was given in portions to 300 ml of ice water. The pH was adjusted to 2-3 with conc. HCl. The water was distilled off and the residue was dissolved in 100 ml of diethyl ether. After about 1 h the product cristallized. The suspension was stirred in an ice bath for 2 h, the solid was filtered off. The crude material was recristallized from 90 ml methanol and dried 12 h at 35°C.

Yield: 5.2 g (39 %) HPLC 98,4 Area-%, m.p. 112-114°C.

1H NMR (δ, DDMSO): 7.19 (CH-O, d), 6.35 (CH=CH2, ddd), 5.44 (CH=CH2, dd), 5.48 (CH=CH2, dd), aromatic signals at 7.0-8.1.

Example 4

Acetic acid 1-(1-benzenesulfonyl-1H-indol-2-yl)-allyl ester

To a solution of 2.9 g (10 mmol) of 1-benzenesulfonyl-1H-indole-2-carbaldehyde (synthesized analogous to M.G. Saulnier, G.W. Gordon, J.Org.Chem.; 47; 5; 1982, 757-761) in 10 ml of tetrahydrofuran was added 6.5 ml of vinylmagnesium chloride 1.7 M solution in THF at -20°C within 1 h. The temperature increased to 0°C within 30 min and kept at this temperature for 20 min. To the suspension 1.3 ml acetic anhydride (14 mmol was added at 0°C within 15 min. The cooling bath was removed and after stirring for 1 h at 20°C 10 ml water was added at 10-15°C . The mixture was stirred for an additional 1 h at 20°C. The phases were separated, and the aqueous phase was extracted with 20 ml of ethyl acetate. The combined organic phases were washed with 20 ml of brine, dried on sodium sulfate and rotary evaporated (35°C, 12 mbar). The crude material was purified by liquid chromatography (eluent isohexane/ethyl acetate 9:1).

Yield: 3.9 g, with a 60% purity according to NMR analysis.

Example 7

Removal of sulfonyl protecting group

A solution of 0.83 g of 9-benzenesulfonyl-9H-carbazol-4-ol (2.57 mmol) in 18 ml of tetrahydrofuran was treated with 2.88 g of potassium tert.butoxide (25.7 mmol) and the suspension stirred at room temperature under argon over night. Then 2N hydrochloric acid solution was added until the pH was 3 and the resulting brown solution was partitioned between 20 ml of tert.butyl methyl ether and 5 ml of water. After drying on sodium sulfate, the organic phase was rotary evaporated (50 °C/10 mbar) to give 500 mg of a dark oil, which according to HPLC analysis (Symmetry C8 column 5 µm 250x4.6 mm, eluted with a mixture of phosphate buffer at pH 7/acetonitrile/water 2:1:7 (40%) and acetonitrile (60%); retention time 4.2 min) had 70% content of 4-hydroxy-9H-carbazole.

1H NMR (δ, $CDCl_3$): 5-5.5 (OH, very broad), 6.5 (1H, d), 8.0 (NH, broad), other aromatic signals at 6.9-8.2.

Treatment of the oil with charcoal (Darco KB-B) in methanol for 1 h at room temperature, filtration and evaporation afforded 4-hydroxy-9H-carbazole as a light brown solid, which could be purified by crystallization from toluene.

Example 8

Synthesis of 9-benzenesulfonyl-9H-carbazol-4-ol starting from crystallized acetic acid 1-(1-benzenesulfonyl-1H-indol-2-yl)-allyl ester

16.60 g of acetic acid 1-(1-benzenesulfonyl-1H-indol-2-yl)-allyl ester (46.7 mmol, crude quality) were crystallized from 20 ml of diisopropyl ether and 10 ml of hexane at 2°C. Filtration afforded 12.7 g (76%) of pure acetic acid 1-(1-benzenesulfonyl-1H-indol-2-yl)-allyl ester as slightly beige crystals with a m.p. of 81-84°C. 9.953 g of this material were subjected to the cyclocarbonylation reaction in analogy to example 1, affording after work-up 10.62 g of acetic acid 9-benzenesulfonyl-9H-carbazol-4-yl ester as a light brown oil with a purity 91% according to HPLC analysis (94.4% isolated yield). 10.50 g of this material was subjected to saponification without further purification in analogy to example 6, affording 9.60 g of 9-benzenesulfonyl-9H-carbazol-4-ol as an orange-brown crystalline material with a 85% purity according to HPLC. Thus, the overall yield over both steps was 90.8%.

the residue was dissolved in a mixture of 236 ml THF and 236 ml 5 N sodium hydroxide solution and stirred for 18 h at 30°C. It was cooled to 20°C and the phases were separated. The water phase was extracted with 300 ml of ethyl acetate, and the combined organic phases were washed with 2 x 300 ml of brine, dried (Na_2SO_4), and rotary evaporated (T_{bath} 40°C, 20 mbar). The resulting brown oil was stirred in 700 ml diethyl ether for 1 h at 20°C, the product crystallized. The suspension was stirred 1 h in an ice bath, the product was filtered under suction, and washed with 50 ml cold diethyl ether. The substance was dried at 50°C for 6 h.

Yield: 18,7 g (67.5 %) of 9-benzenesulfonyl-4-oxiranylmethoxy-9H-carbazole as light brown solid, m.p. 107/108-110°C.

1H NMR (δ, DDMSO): 4.09 (CH2-O, dd), 4.56 (CH2-O, dd), 3.49 (CH-O, cycle, dddd), 2.80 (CH2-O, cycle, dd), 2.90 (CH2-O, cycle, dd), aromatic signals at 6.9-8.3.

From the mother liquor additional 5,3 g substance was isolated, m.p. 100/103-107°C.

Example 12

1-(9-Benzenesulfonyl-9H-carbazol-4-yloxy)-3-{benzyl-[2-(2-methoxy-phenoxy)-ethyl]-amino}-propan-2-ol

7.4 g of benzyl-[2-(2-methoxy-phenoxy)-ethyl]-amine (29 mmol) were dissolved in 47 ml ethanol. To the stirred solution 10 g of 9-benzenesulfonyl-4-oxiranylmethoxy-9H-carbazole (26 mmol) were added and the mixture was heated under reflux for 15 h. The boiling solution was treated with 1 g of activated carbon for 30 min. The activated carbon was filtered off in the heat, and washed with 20 ml ethanol. The ethanol was rotary evaporated (T_{bath} 40°C, 20 mbar) and the crude material purified by liquid chromatography (eluent toluene/ethyl acetate 4:1), the pure fractions were collected and rotary evaporated (40°C/15 mbar).

Yield: 11.1 g (67 %).

1H NMR (δ, DDMSO): 4.21 (-O-CH2-CH-O, dd), 4.09 (-O-CH2-CH-O, m), 4.10 (-O-CH2-CH-O, m), 4.91 (-OH, d), 2.72 (-O-CH-CH2-N, dd), 2.86 (-O-CH-CH2-N, dd), 3.72 (N-CH2-Ph, d), 3.81 (N-CH2-Ph, d), 2.89 (N-CH2-CH2-O, m), 3.99 (N-CH2-CH2-O, t), 3.64 (-O-CH3, s), aromatic signals at 6.7-8.3.

Example 16

1-(9H-carbazol-4-yloxy)-3-[2-(2-methoxy-phenoxy)-ethylamino]-propan-2-ol (carvedilol)

10 g of 1-[Benzyl-[2-(2-methoxy-phenoxy)-ethyl]-amino]-3-(9H-carbazol-4-yloxy)-propan-2-ol (20 mmol) were dissolved in 80 ml methanol. 1 g of Pd-C (10%) were added and the suspension was warmed to 50°C. The mixture was hydrogenated at normal pressure for about 7 hours. The Pd-catalyst was filtered under suction and washed with 25 ml of hot methanol. 80 ml of methanol were distilled off and the residue was cooled to 0°C and hold at this temperature for 6 h. The product was filtered and washed twice with 3 ml cold methanol. The substance was dried at 60°C for 12 h.

Yield: 7.5 g (91%), m.p. 112-114°C.

followed by saponification of the compound of formula (III).

2. The process according to claim 1, wherein X is N-Z.

3. The process according to any of claims 1-2, wherein Z is SO_2R^a and R^a is phenyl.

4. The process according to any of claims 1-3, wherein R^1 and R^2 together with the ring carbon atoms to which they are attached form a phenyl ring.

5. The process according to any of claims 1-4, wherein R^3 is methyl or phenyl.

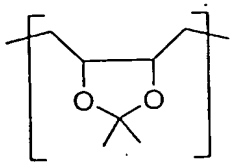
6. The process according to any of claims 1-5, wherein the cyclocarbonylation reaction is carried out in the presence of a base, an anhydride and a catalyst comprising a transition metal compound and a ligand.

7. The process according to any of claims 1-6, wherein the transition metal compound is a palladium salt.

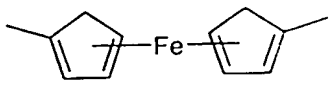
8. The process according to claim 7, wherein the transition metal compound is selected from a group consisting of $Pd(OAc)_2$, Pd_2dba_3, $PdCl_2$, $Pd_2Cl_2(\pi\text{-allyl})_2$, $PdCl_2(NCMe)_2$, $[Pd(NCMe)_4](BF_4)_2$ or Pd/C.

9. The process according to claim 8, wherein the transition metal compound is $Pd(OAc)_2$.

10. The process according to any of claims 1-9, wherein the ligand is $P(R^5)(R^6)(R^7)$ or $(R^5)(R^6)P\text{-}(Y)\text{-}P(R^5)(R^6)$ wherein R^5, R^6 and R^7 each independently are C_{1-8}-alkyl, cyclohexyl, benzyl, naphthyl, 2- or 3-pyrrolyl, 2- or 3-furyl, 2- or 3-thiophenyl, 2- or 3- or 4-pyridyl, phenyl or phenyl which is substituted by C_{1-4}-alkyl, C_{1-4}-alkoxy, halogen, trifluoromethyl, lower alkylydenedioxy or phenyl and Y is binaphthyl, 6,6'-dimethyl- or 6,6'-dimethoxybiphenyl-2,2'-diyl, or one of the groups $-(CH_2)_n-$, $-CH_2CH_2\text{-}P(C_6H_5)\text{-}CH_2CH_2-$,



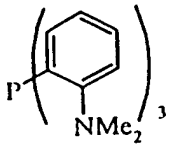
or



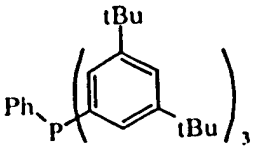
(IV)

and n is a number of 1 – 8.

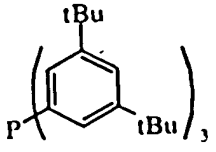
11. The process according to any of claims 1-9, wherein the ligand is selected from a group consisting of triphenylphosphine, and



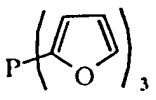
P(o-DMA-Ph)$_3$



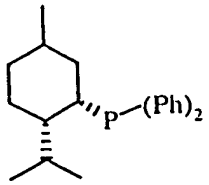
PPh(3,5-tBu-Ph)$_2$



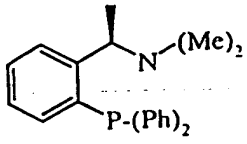
P(3,5-tBu-Ph)$_3$



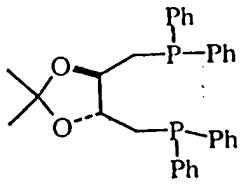
P(2-Furyl)$_3$



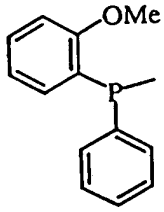
NMDPP



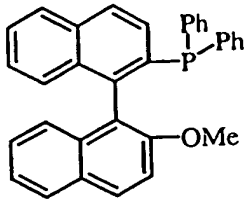
AMPHOS



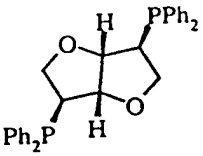
DIOP



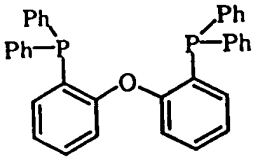
PAMP



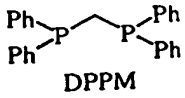
MOP



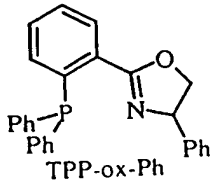
(S,S)-DDPPI



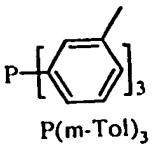
DPEphos



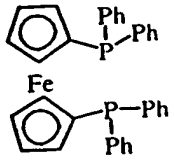
DPPM



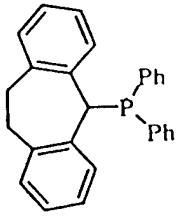
TPP-ox-Ph



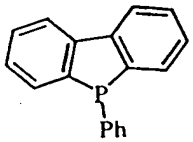
P(m-Tol)$_3$



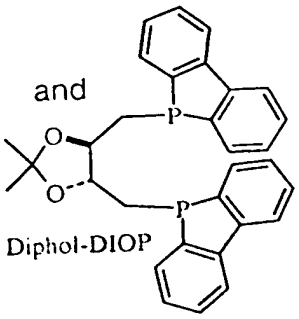
DPPF



TROPP-Ph

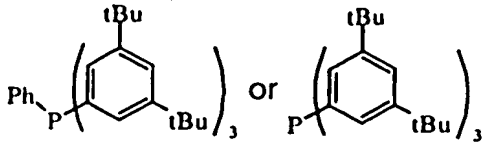


PPh(Diphol)



Diphol-DIOP

12. The process according to any of claims 1-9, wherein the ligand is triphenylphosphine,



$PPh(3,5\text{-}tBu\text{-}Ph)_2$ $P(3,5\text{-}tBu\text{-}Ph)_3$

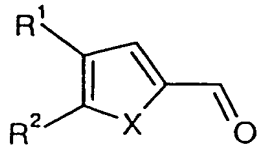
13. The process according to any of claims 1-12, wherein the cyclocarbonylation reaction is carried out in the presence of a base selected from the group consisting of tri-alkyl-amines, di-alkyl-aryl-amines, pyridines, alkyl-N-piperidines, sodium hydroxide, potassium hydroxide or salts of carbonic acids.

14. The process according to any of claims 1-12, wherein the cyclocarbonylation reaction is carried out in the presence of triethylamine.

15. The process according to any of claims 1-14, wherein the cyclocarbonylation reaction is carried out in the presence of an anhydride of the formula $(R^4(C=O))_2O$, wherein R^4 is as defined in claim 1.

16. The process according to any of claims 1-14, wherein the cyclocarbonylation reaction is carried out in the presence of an anhydride selected from acetic anhydride, propionic anhydride, butyric anhydride, isobutyric anhydride, pivalic anhydride and benzoic anhydride.

17. The process according to claims 1-16, wherein the compounds of formula (II) are prepared by reaction of compounds of formula (V)

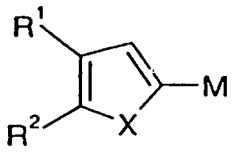


(V)

wherein R^1, R^2 and X are as defined above;

with a reagent of the formula vinyl-metal-X with –metal-X being –MgCl, -MgBr, -MgI or -Li, followed by reaction with an acid derivative selected from a group consisting of $(R^3\text{-}CO)_2O$, or $R^3\text{-}(CO)\text{-}Hal$, wherein R^3 is as defined in claims 1 to 16 and Hal is Cl or Br.

18. The process according to claims 1-15, wherein the compounds of formula (II) are prepared by reaction of compounds of formula (VI)



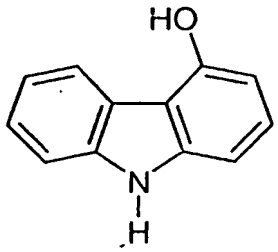
(VI)

wherein R^1, R^2 and X are as defined above and M is –MgCl, -MgBr, -MgI or –Li; with acrolein, followed by reaction with an acid derivative selected from a group consisting of $(R^3\text{-}CO)_2O$ or $R^3\text{-}(CO)\text{-Hal}$, wherein R^3 is as defined in claims 1 to 17 and Hal is Cl or Br.

19. The process according to any of claims 1-17, wherein the saponification reaction is carried out in a biphasic mixture of sodium hydroxide in toluene or in a homogeneous mixture of sodium methylate in methanol.

20. The process according to any of claims 1-19, wherein R^1 and R^2 together with the ring carbon atoms to which they are attached form a phenyl ring; X is N-Z and Z is as defined in claims 1 or 3.

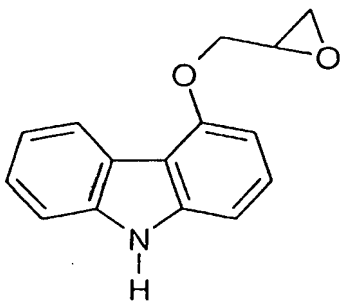
21. The process according to claim 20, wherein the N-protected 4-hydroxycarbazole of formula (I) is converted into 4-hydroxycarbazole of formula (XI)



(XI)

by deprotection.

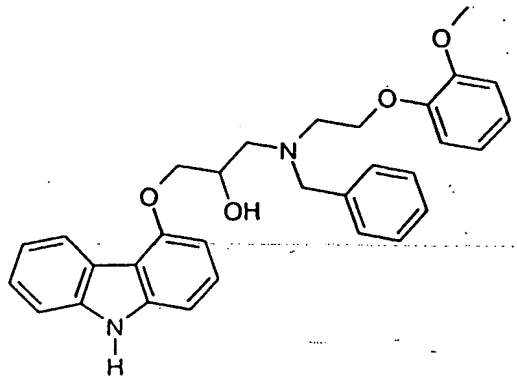
22. The process according to claim 21, wherein the 4-hydroxycarbazole of formula (XI) is converted into a compound of formula (XII)



(XII)

by reaction with epichlorohydrin under basic conditions.

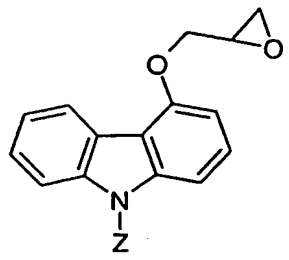
23. The process according to claim 22, wherein a compound of formula (XII) is converted into a compound of formula (IX)



(IX)

by reaction with benzyl-[2-2(2-methoxy-phenoxy]-ethylamine.

24. The process according to claim 20, wherein the N-protected 4-hydroxycarbazole of formula (I) is converted into a compound of formula (VII)

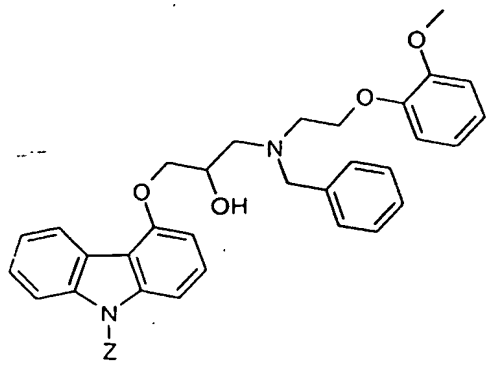


(VII)

wherein Z is as defined in claim 1;

by reaction with epichlorohydrin under basic conditions.

25. The process according to claim 24, wherein a compound of formula (VII) is converted into a compound of formula (VIII)

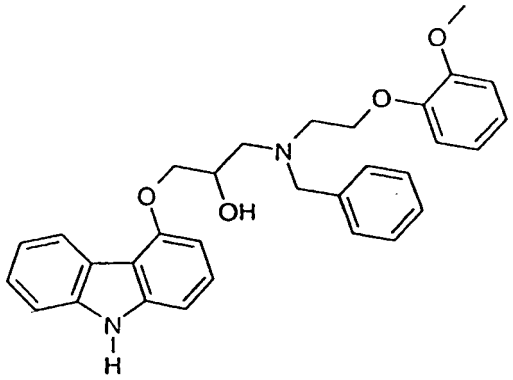


(VIII)

wherein Z is as defined in claim 1;

by reaction with benzyl-[2-(2-methoxy-phenoxy]-ethyl-amine.

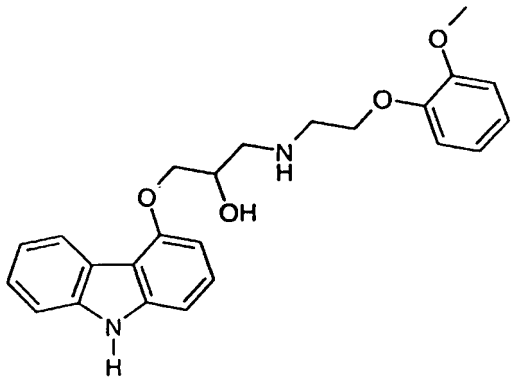
26. The process according to claim 25, wherein a compound of formula (VIII) is converted into a compound of formula (IX)



(IX)

by deprotection.

27. The process according to any of claims 23 or 26, wherein a compound of formula (IX) is converted to 1-(4-carbazolyloxy)-3-[2-(2-methoxyphenoxy)ethylamino]-2-propanole of formula (X)



(X)

by hydrogenation.

28. The process according any of claims 1-27 for the preparation of 1-(9H-carbazol-4-yloxy)-3-{[2-(2-methoxyphenoxy)ethyl]amino}-2-propanol comprising:

a) cyclocarbonylation of acetic acid 1-(1-benzenesulfonyl-1H-indol-2-yl)allyl ester or benzoic acid 1-(1-benzenesulfonyl-1H-indol-2-yl)-allyl ester to give acetic acid 9-benzenesulfonyl-9H-carbazol-4-yl ester;

b) saponification of acetic acid 9-benzenesulfonyl-9H-carbazol-4-yl ester to give 9-benzenesulfonyl-9H-carbazol-4-ol;

c) reaction of 9-benzenesulfonyl-9H-carbazol-4-ol with epichlorohydrin under basic conditions to give 9-benzenesulfonyl-4-oxiranylmethoxy-9H-carbazole;

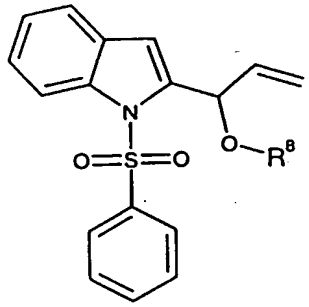
d) reaction of a compound of formula 9-benzenesulfonyl-4-oxiranylmethoxy-9H-carbazole with benzyl-[2-(2-methoxy-phenoxy]-ethyl-amine to give a 1-(9-benzenesulfonyl-9H-carbazol-4-yloxy)-3-{benzyl-[2-(2-methoxy-phenoxy)ethyl]-amino}-propan-2-ol;

e) deprotection of 1-(9-benzenesulfonyl-9H-carbazol-4-yloxy)-3-{benzyl-[2-(2-methoxy-phenoxy)ethyl]-amino}-propan-2-ol under basic conditions to give 1-{benzyl-[2-(2-methoxy-phenoxy)-ethyl]-amino}-3-(9H-carbazol-4-yloxy)-propan-2-ol;

f) hydrogenation of 1-{benzyl-[2-(2-methoxy-phenoxy)-ethyl]-amino}-3-(9H-carbazol-4-yloxy)-propan-2-ol in an organic solvent to give 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-2-propanol.

29. The use of a process according to any of claims 1-28 for the preparation of 1-(4-carbazolyloxy)-3-[2-(2-methoxyphenoxy)ethylamino]-2-propanole.

30. A compound of formula (IIa)



(IIa)

wherein R^8 is hydrogen, acetyl or benzoyl.

31. The invention as described hereinbefore.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
1 August 2002 (01.08.2002)

PCT

(10) International Publication Number
WO 02/059089 A3

(51) International Patent Classification[7]: C07D 209/12, 209/88, 405/12

(21) International Application Number: PCT/EP02/00583

(22) International Filing Date: 22 January 2002 (22.01.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
01101584.9 25 January 2001 (25.01.2001) EP

(71) Applicant: F. HOFFMANN-LA ROCHE AG [CH/CH]; 124, Grenzacherstrasse, CH-4070 Basle (CH).

(72) Inventors: SCALONE, Michelangelo: 14, Baslerstrasse, CH-4127 Birsfelden (CH). ZEIBIG, Thomas: 3, Schlesierstrasse, 67112 Mutterstadt (DE).

(74) Agent: WITTE, Hubert; 124 Grenzacherstrasse, CH-4070 Basle (CH).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
with international search report
before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:
31 October 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PROCESS FOR THE PREPARATION OF HETEROCYCLIC INDENE ANALOGS

(57) Abstract: The present invention is concerned with a novel process for the preparation of compounds of formula (I) wherein R^1, R^2 and X are as defined in the specification, comprising cyclocarbonylation of a compound of formula (II) wherein R^1, R^2, R^4 and X are as defined in the specification, to produce a compound of formula (III) wherein R^1, R^2, R^4 and X are as defined in the specification, followed by saponification.

WO 02/059089 A3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/00583

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D209/12 C07D209/88 C07D405/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MASAKAZU IWASAKI ET AL.: "Palladium-catalyzed cyclocarbonylation of 3-(heteroaryl)allyl acetates" JOURNAL OF ORGANIC CHEMISTRY., vol. 56, - 1991 pages 1922-1927, XP002209122 AMERICAN CHEMICAL SOCIETY. EASTON., US ISSN: 0022-3263 * complete document *	1,7
P,X	EP 1 078 923 A (F. HOFFMANN-LA ROCHE AG) 28 February 2001 (2001-02-28) * complete document *	1,7-19

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 August 2002	21/08/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Van Bijlen, H

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 02/00583

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1078923 A	28-02-2001	EP 1078923 A2	28-02-2001
		CN 1282741 A	07-02-2001
		JP 3278649 B2	30-04-2002
		JP 2001048876 A	20-02-2001
		JP 2002155079 A	28-05-2002
		US 2002077488 A1	20-06-2002
		US 6291685 B1	18-09-2001
		US 2002010345 A1	24-01-2002